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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,798	09/20/2006	**Allan Kent Nielsen**	10576.204-US	1316

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EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	**PAPER NUMBER**
1656	

NOTIFICATION DATE	DELIVERY MODE
02/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents-US-NY@novozymes.com

Office Action Summary	Application No.	Applicant(s)	
	10/593,798	NIELSEN ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This Application is a 371 national stage of PCT/DK2005/000236 filed on April 07, 2005 which claims priority from US provisional Application 60/562396 filed on April 14, 2004. Claims 1-57 are cancelled. Claims 58-77 are present for examination.

Information Disclosure Statement

The information disclosure statement filed on September 20, 2006 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature.

Oath/Declaration

The oath or declaration submitted on September 20, 2006 has been reviewed and is in compliance with 37 CFR 1.56.

Drawings

The drawings were received on September 20, 2006. These drawings are accepted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include: **a**. Actual reduction to practice; **b.** Disclosure of drawings or structural chemical formulas;

c. Sufficient relevant identifying characteristics such as

i. Complete structure,

ii. Partial structure,

iii. Physical and/or chemical properties or

iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;

d. Method of making the claimed invention; **e.** Level of skill and knowledge in the art and **f.** Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed as they relate to the issues mentioned above.

Claims 58-67 are directed to a genus of mutant cells from any prokaryotic source or Bacillus species comprising any mutation and having reduced expression level of a genus of YusZ and/or YusX and/or YusY polypeptides and homologues and polynucleotide sequences

encoding the same with an ability to secrete a higher amount of a polypeptide of interest (claim 58-67) compared to non-mutated cells. Furthermore the claims are drawn to methods of using the above genus of cells (claims 68-77), with an ability to secret higher amounts of at least one heterologous polypeptide of interest when compared to a non-mutated cell.

However the specification only discloses the reduction into practice of specific strains of *Bacillus subtilis* comprising specific mutations such as a deletion of the *yusZ* of SEQ ID NO: 1 and/or a deletion of the *yusX* of SEQ ID NO: 3 or a specific strain of *Bacillus licheniformis* further comprising a deletion of the *yusZ* of SEQ ID NO: 24 that secret a higher amount of a polypeptide of interest (in this case either an alpha-amylase, a protease).

Applicants have not reduced to practice any strain of bacteria comprising any mutations or other means of reducing the expression of the above polypeptides. Furthermore Applicants have not reduced into practice the claimed genus of mutant prokaryotic cells comprising the genus of YusZ and/or YusX polypeptide homologues and/or YusY polypeptide homologues with up to 30% variation in sequence or mutated polynucleotide sequences encoding the same with an ability to secrete a higher amount of a polypeptide of interest compared to non-mutated cells.

The specification refers only to a *B. subtilis* wherein the *yusz* of SEQ ID NO: 1 and/or *yusx* of SEQ ID NO: 3 were deleted by homologous recombination (examples 1 and 3). Furthermore examples 2 and 4 show that a higher level of a desired protein (alpha-amylase) was secreted as a result of the above deletion. Furthermore example 5 teaches deletion of *yusz* (SEQ ID NO: 4) from a specific strain of *B. licheniformis*. Said *yusz* deletion results in higher level of a protein secretion (a protease) in the said *B. licheniformis* compared to non-mutated cells.

The instant claims encompass any prokaryotic cell comprising any mutation and a deletion of any homologue gene with 70% identity to the yusz, yusx gene discussed above (thus include open reading frames with up to 30% variation) in any prokaryotic cell or any Bacillus species wherein said mutation results in cell capable of secreting higher levels of secretion of at least one desired protein. However the specification does not disclose the broad scope of any prokaryotic cell comprising any mutation and variant of yusz (SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants of SEQ ID NO 24 encoding SEQ ID NO: 25) or variants of yusx (SEQ ID NO: 3 encoding SEQ ID NO: 4) that result in the desired effect. The specification does not describe the structure of any or all mutations in any prokaryotic cell including all *yusz, yusx* from any prokaryotic cell or from any Bacillus or species thereof claimed in claim 61 and/or the assurance that deleting a sequence with 70% identity thereto would result in the desired effect.

For example, on page 11 last paragraph the specification states:

"… a functional homologue of the YusZ or YusX protein is a protein, which when expressed at a reduced level in a cell, leads to an increased secretion of a heterologous polypeptide, preferably an enzyme such as an alpha-amylase, when compared with an isogenic having a normal expression of the YusZ or YusX protein…"

However the above functional limitation does not allow a skilled artisan to predict the structure function correlation for the genus of *yusz, yusx* and/or *yusy* homologues with up to 30% sequence divergence. The specification does not disclose any common identifying characteristics for the above genus. This is because at the time the instant invention was disclosed other than the specific sequences of *yusz* (SEQ ID NO: 1 encoding 2 or SEQ ID NO: 24 encoding 25), *yusx* (SEQ ID NO: 3 encoding SEQ ID NO: 4) the art does not teach the structure and function of

sequences with at least 70% identity wherein deletion of these sequences results in increased level secretion of a desired protein from any prokaryotic cell or Bacillus species.

However at the time of the instant invention the art does not teach the function of the protein encoded by these genes, thus one of skill cannot predict how to identify a functional homologue. Furthermore the specification does not provide an alignment of homologues of the above sequences genes or proteins or domains that are common to all the above genes where such domains can be relied upon to identify the function of these genes.

Furthermore at the time the instant invention was disclosed there was no art recognized correlation between any structural homologue with up to 30% variation (to the *yusz* of SEQ ID NO: 1 encoding 2 or SEQ ID NO: 24 encoding 25 and/or the *yusx* of SEQ ID NO: 3 encoding SEQ ID NO: 4) and/or the *yusy* of SEQ ID NO: 5 encoding the polypeptide of SEQ ID NO: 6), and any specific activity.

Thus one of skill in the art cannot predict the results obtained by deleting or reducing the expression of polypeptides showing only 70% sequence identity to the YusZ and/or YusX.

The level of skill in the art is such that one of skill would not be able to identify without further testing which homologues within the broad genus of 70% identity to *yusz* (SEQ ID NO: 1 encoding 2 or SEQ ID NO: 24 encoding 25), *yusx* (SEQ ID NO: 3 encoding SEQ ID NO: 4) would result in secretion of higher levels of proteins when deleted in any prokaryotic cell or any Bacillus species.

Based on the lack of knowledge and predictability in the art, those skilled in the art would not conclude that applicants were in possession of the claimed genus of prokaryotic cells or genus of Bacillus species with polypeptides/polynucleotides sequences with up to 30%

variation to *yusz* (SEQ ID NO: 1 encoding 2 or SEQ ID NO: 24 encoding 25), *yusx* (SEQ ID NO: 3 encoding SEQ ID NO: 4) and/or the *yusy* of SEQ ID NO: 5 encoding the polypeptide of SEQ ID NO: 6) wherein deletion of these sequences results in increased level of secretion of a desired protein or the method of using the same.

Furthermore at the time of the instant invention the art does not teach the physiological role of the protein encoded by these genes, thus one of skill cannot predict how to identify a functional homologue without undue amount of experimentation.

Claims 58-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific strains of *Bacillus subtilis* comprising a deletion of the *yusZ* of SEQ ID NO: 1 or 24 and/or a deletion of the *yusX* of SEQ ID NO: 3 or a specific strain of *Bacillus licheniformis* further comprising a deletion of the *yusZ* of SEQ ID NO: 24 that secret a higher amount of a polypeptide of interest (in this case either an alpha-amylase, a protease), it, does not reasonably provide enablement for:

a) any mutant prokaryotic cell having any mutation and a reduced level of expression of above polypeptides,

b) any other means of reducing the expression of the above polypeptides,

c) any prokaryotic cell comprising the genus of YusZ and/or YusX and/or YusY polypeptide homologues with up to 30% variation in sequence or mutated polynucleotide sequences encoding the same with an ability to secrete a higher amount of a polypeptide of interest compared to non-mutated cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized ln re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any prokaryotic microorganism or Bacillus species comprising a reduced expression level of any homologues of YusZ and/or YusX and/or YusY polypeptides and polynucleotide sequences encoding the same with 70% sequence identity to the corresponding wild type sequences wherein said microorganisms show secretion of a higher amount of a protein of interest compared to non-mutated cells.

Furthermore the claims are drawn to methods of using the above genus of microorganisms (claims 68-77), to produce a polypeptide of interest.

The specification provides guidance and examples for only a *B. subtilis* wherein the *yusz* of SEQ ID NO: 1 and/or *yusx* of SEQ ID NO: 3 were deleted by homologous recombination (examples 1 and 3). Furthermore examples 2 and 4 show that a higher level of a desired protein (alpha-amylase) was secreted as a result of the above deletion. Furthermore example 5 teaches deletion of *yusz* (SEQ ID NO: 4) from a specific strain of *B. licheniformis*. Said *yusz* deletion results in higher level of a protein secretion (a protease) in the said *B. licheniformis* compared to non-mutated cells.

The instant claims encompass any modified prokaryotic cell having any type of modification or Bacillus species comprising any polypeptide or polynucleotide encoding the

same that shows up to 30% variation relative to the *yusz, yusx* and/or *yusy* genes identified in *B. subtilis* or *B. licheniformis* wherein said modification results in cell capable of secreting higher levels of at least one desired protein.

However, the specification does not teach the specific structure of any gene that shows 70% sequence identity to the *yusZ* of *B. subtilis* or *B. licheniformis* (SEQ ID NO: 1 or 24) and/or to *yusX* of SEQ ID NO: 3 and/or to the *yusy* of SEQ ID NO: 5 or the encoded protein. Furthermore the specification does not teach reducing the expression of the encoded protein by any other means other than deleting the corresponding gene(s).

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue.

Such experimentation entails deciphering whether or not a polynucleotide sequence and encoded protein comprising up to 30% variation compared to any specific wild type sequence (in this case *yusz* of SEQ ID NO: 1 or 24 and/or the *yusx* of SEQ ID NO: 3 and/or to the *yusy* of SEQ ID NO: 5) would have the identical physiological role in a cell such that its deletion would result in the same biological effect i.e. secretion of a higher amount of a desired protein.

However, identifying a sequence with up to 30% sequence identity from any prokaryotic cell or from any Bacillus species and determining whether the sequence has the same biological effect is well outside the realm of routine experimentation.

This is primarily because the art or the specification do not provide guidance regarding the biological role of *yusZ* of SEQ ID NO: 1 or 24 and/or the *yusX* of SEQ ID NO: 3 and/or to the *yusy* of SEQ ID NO: 5) (see page 1 background of the instant specification) in order to

reliably decipher the physiological role a sequence with 70% identity to the above sequences have. Furthermore the specification does not teach that deletion (or reduced expression) of these sequences would result in higher secretion of a desired protein.

It should be noted that the degree of structural homology (in this case 70% identity) does not necessarily guarantee the same function (see for example Bork et al. Predicting functions from protein sequence-where are the bottlenecks?). Bork et al. state that while predicting function based on sequence analysis is a powerful tool, relying solely on sequence data may lead to creation and propagation of assignment errors.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific sequences that have the same biological role as *yusZ* of SEQ ID NO: 1 or 24 and/or the *yusX* of SEQ ID NO: 3 and/or to the *yusy* of SEQ ID NO: 5 where deletion of these sequence(s) in a microorganism will results in secretion of a higher level of a desired protein. Without such a guidance, the experimentation left to those skilled in the art is undue.

Conclusion: No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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2/5/2010

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